ULNAR NEUROPATHY AS A FIRST SIGN OF HIV INFECTION

A diagnostic challenge for leprosy endemic countries

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Mycobacterium leprae and HIV are two infectious agents capable of infecting peripheral nerves and, as a result, inducing peripheral neuropathy. In leprosy endemic countries, more refined diagnostic procedures than are currently available are urgently needed to accurately a differential diagnosis between the peripheral neuropathies presenting in both HIV and leprosy since mononeuropathy simplex and multiplex as well as polyneuropathy are known to occur in both diseases (Jardim et al., 2003). Pure neural leprosy (PNL), for example, presents a particularly difficult diagnostic challenge. PNL patients have nerve deficit and/or enlargement of peripheral nerves with or without tenderness in the absence of any sign of skin disease or history of skin patches (Talwar et al., 1992). In this study, the case of a seropositive HIV patient admitted to our Leprosy Outpatient Clinic under suspicion of leprosy neuropathy is described.

CASE

A 20-year-old HIV seropositive woman complained of paresthesia in the left ulnar nerve that had begun nine months before her referral to the Leprosy Outpatient Clinic in April 2005, at which time no pain or muscle weakness was reported. In May 2004, the patient tested seropositive for HIV during a screening prior to a myomectomy but had not received any anti-HIV treatment due to lack of symptoms. In August 2004, the patient's viral load was 12,000 RNA copies/ml. However, when the nerve biopsy was performed on April 28, 2005, her viral load was 22,000 RNA copies/μl, having almost doubled during eight months.

At the outset, clinical examination revealed reduced pain and temperature sensation in the ulnar nerve. What was particularly noteworthy was the absence of any skin lesions suggestive of leprosy or of any thickening or tenderness of the peripheral nerves. But although the deep tendon reflexes were normal, muscle strength diminished in the ulnar nerve territory (Grade 4 on the MRC scale); and electrophysiological studies were consistent with axonal ulnar neuropathy (Table 1). A special approach is necessary to detect autonomic abnormalities, which can be studied by measuring the transient fall in fingertip blood flow after an inspiratory gasp or the sympathetic skin response that mediates the sudomotor function (Shahani et al., 1984). To test the autonomic function, the skin vasomotor reflex (VMR) was evaluated by means of the LASER Doppler velocimetry (PERIMED 5000™, Sweden), as described by Illarramendi et al. (2005). Indicative of normal sympathetic conduction, the VMR in both the second and fifth right fingers in response to the inspiratory gasp was normal. Nevertheless, the patient demonstrated a reduced VMR (–72.915) with slightly below normal values (–73.157) on the fifth left finger, suggesting that fine fibers had been affected.

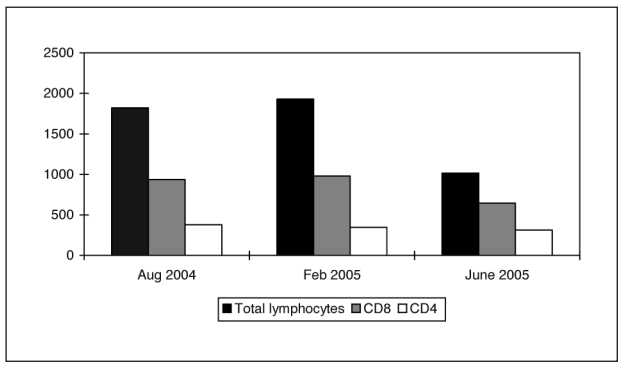

Fig 1. Blood lymphocyte count progression during the evaluation period. CD4 lymphocytes progressively decreased and remained below 400 cells/ml.

NEUROPATIA ULNAR COMO SINAL INICIAL DA INFECÇÃO PELO HIV: UM DESAFIO DIAGNÓSTICO EM PAÍSES ENDÊMICOS DE HANSENÍASE

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Table 1. Nerve conduction studies.

	Amplitude (μV)	Latency (ms)	Nerve velocity (m/s)
Sensory nerves			
Right radial	16.3	1.8	54.3
Right median	18.6	3.7	47.8
Right ulnar	11.3	2.1	56.1
Right sural	12.0	2.8	52.8
Left radial	21.3	1.4	73.0
Left median	16.0	2.9	44.5
Left ulnar	0	0	0
Left sural	32.0	2.7	51.5
Motor nerves			
Right ulnar			
Wrist	5.8	3.0	
Elbow ↓	4.8	8.0	54.2
Elbow ↑	4.8	10.2	55.1
Arm	4.8	11.5	78.5
Right median			
Wrist	11.5	3.6	
Elbow	8.6	8.8	55.8
Right fibular			
Ankle	6.8	3.4	
Knee	5.9	10.0	57.6
Left ulnar			
Wrist	0	0	
Elbow ↓	0	0	0
Elbow ↑	0	0	0
Arm	0	0	0
Left median			
Wrist	8.2	3.4	
Elbow	7.0	8.2	75.6
Left fibular			
Ankle	5.3	3.0	
Knee	4.2	10.4	51.5

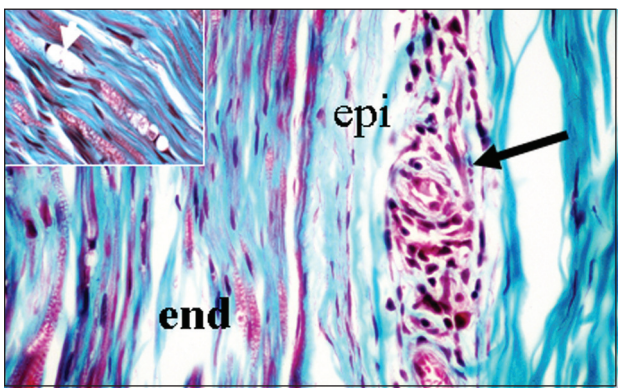

Fig 2. Focal inflammatory infiltrate surrounding an epineurial microvessel. (Gomori's trichrome. Scale bar: 40 μm). The inset shows the presence of myelin ovoids along degenerating fibers in the same fascicle seen in the main frame. (Magnification ×400). epi: epineurium; end: endoneurium.

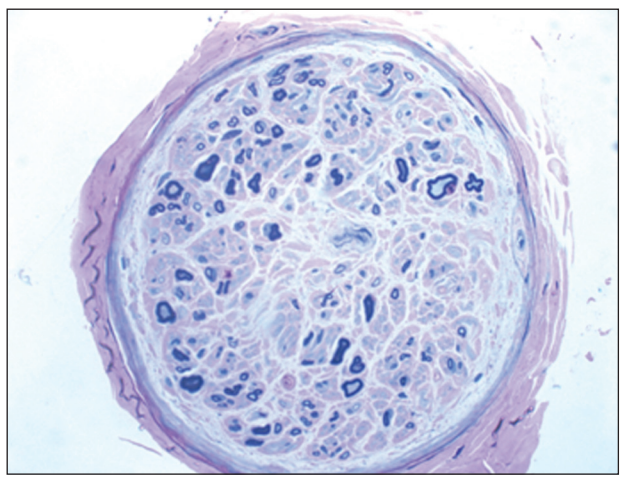

Fig 3. Loss of large and small myelinated fibers in a single nerve fascicle (Semithin section. Toluidine blue staining. Magnification ×400).

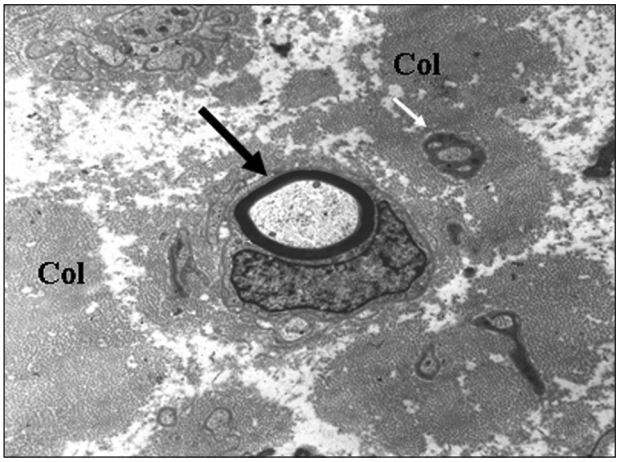

Fig 4. Single myelinated fiber (black arrow) surrounded by an increased number of collagen fibers (col) and by Schwann cell profiles with collagen pockets in the absence of axons (white arrows). Electronmicrography ×15000.

During the neurological assessment period, all of the following results were likewise normal: the blood count, erythrocyte sedimentation rate, glucose, urea, electrolytes (including plasma calcium concentration), creatinine values, thyroid function test, liver function test, and chest radiography. Slit skin smears from six sites failed to show any acid-fast bacilli. ELISA tests for cytomegalovirus, syphilis infection, hepatitis C and B, HTLV-1, and anti-PGL-1 antibodies were, again, negative. Figure 1 summarizes the progression of the lymphocyte count.

To confirm diagnosis, a biopsy of the left dorsal cutaneous ulnar nerve was performed. Histopathological examination showed a mild focal inflammatory infiltrate composed of macrophages and lymphocytes. Plasma cells surrounding epineurial microvessels were also seen (Fig 2) together with the loss of large and small myelinated fibers (Fig 3). The presence of myelin ovoids was noticed as well (Fig 2 inset). No acid-fast bacilli were detected; and the PCR for detection of HIV and *M leprae* DNA in the nerve was negative. In addition to increased endoneurial collagen, the ultra-structure study of the nerve fascicle revealed indirect evidence of non-myelinated fiber loss, characterized by the presence of Schwann cell processes involving collagen fibers (collagen pockets) (Fig 4).

DISCUSSION

PNL is a form of the disease in which no cutaneous manifestations are found. On average, neuritic leprosy accounts for roughly 10% of all leprosy cases, being particularly difficult to diagnose if acid-fast bacilli are not found in the skin smears or histological sections of the nerves.

In this regard, PCR has proven to be a very useful tool in confirming PNL diagnoses (Antunes et al., 2006). In previous studies, mononeuritis and mononeuritis multiplex have been the most common PNL presentations (de Freitas, 2007). Besides, ulnar neuropathy, the most frequently-occurring neuropathy in leprosy, may result in the classic hand deformity (claw hand) often associated with this disease. In patients in whom nerve damage occurs in the absence of dermatological lesions, accurately diagnosing PNL is difficult In relation to HIV neuropathies, many types of peripheral neuropathies are seen in HIV patients, but only a few appear to be HIV specific. It appeared that a link may exist between type of neuropathy and the stage of HIV infection. Multiple mononeuropathy (MM) caused by vasculitis occurring in the setting of symptomatic HIV-1 infection has been reported (Sacktor, 2002). The incidence of MM has a bimodal distribution, peaking during early as well as advanced HIV infection. In relatively immunocompetent patients, MM typically presents with dysfunctions attributable to a limited number of peripheral or cranial nerves. The deficits are typically resolved spontaneously over several months, it is postulated that rhere is an autoimmune mechanism, axonal degeneration, and inflammation are seen in nerve biopsy specimens (Polydefkis, 2002; Robinson-Papp J and Simpson DM, 2008) In this clinical form, the main differential diagnosis is vasculitic neuropathy, including its various causes such as HIV, CMV, and herpes zoster.

The case reported in this study is a clear example of a mononeuropathy simplex whose manifestations could be diagnosed as either leprosy or HIV infection. The patient's histopathological findings were directly related to a focal perivascular inflammatory infiltrate accompanied by axonal degeneration and myelinated fiber loss. This is consistent with the Midroni and Bilbao study (1999) describing a perivascular inflammatory infiltrate, with or without vasculitic damage, involving endoneurial or epineurial vessels, axonal degeneration, and the demyelination that tend to occur in this type of HIV neuropathy. Moreover, it is known that Chaunu et al. (1989) previously reported on two asymptomatic, HIV-seropositive patients whose biopsies showed microvessels surrounding epineurial and endoneurial mononuclear cell infiltrations but sparing larger vessels.

In addition to a histopathological study of the affected nerve, a definitive diagnosis requires the amplification of *M leprae*/HIV DNA by means of PCR, clearly applicable to the present case study in which histopathological findings were consistent with the above description. These findings, however, were considered insufficient to definitively diagnose either leprosy or HIV neuropathy (Jardim et al., 2003). Furthermore, given that the histopathological findings were associated to serological positivity with an increasing viral load and decreasing CD4 counts (last count in February 2007: 240) in the peripheral blood and were also consistent with HIV mononeuropathy simplex, our contention is twofold: that this patient represented a case of HIV-provoked ulnar neuropathy and that HIV was capable of clinically mimicking leprosy neuropathy.

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